## *REMARKS*

Claims 28-42, 45, 47, 50, 53-54, 57 and 58-74 are pending in this application.

Claims 1-27 and 43 have previously been canceled without prejudice or disclaimer. Claims 44, 46, 48-49, 51-52 and 55-56 have been canceled without prejudice or disclaimer. Claims 58-74 have been newly added. Claims 28-31, 36-42, 45, 47, 50, 53-54 and 57 have been amended. Claims 28-42, 47-50, 52, 54, 57 and 58-59 have been rejected.

Claims 44-45, 48-49 and 52 are withdrawn from consideration as being directed to a non-elected species. Applicants note that upon allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 C.F.R. § 1.141.

Claims 1-27, 43-44, 46, 48-49, 51-52 and 55-56 have been canceled without prejudice or disclaimer, and claims 28-31, 36-42, 45, 47, 50, 53-54 and 57 have been amended, for the sole reason of advancing prosecution. Applicants, by canceling or amending any claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

The Examiner is thanked for indicating claims 45 and 53 allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. Accordingly, new claim 58 has been presented and corresponds to claim 45 written in independent form and including all of the limitations of base claim 28. New

claims 69-72 are each directly or indirectly dependent on new independent claim 58. With regard to allowable claim 53, claim 53 is dependent on claim 50. Claim 50 has been amended to incorporate the limitations of claim 53, i.e., to recite that the protein or polypeptide is Copaxone. In addition, claim 53 has been amended to recite that the amphipathic lipid of claim 50 is selected from the group consisting of phosphatidylethanolamine (PE), a carbamate-linked uncharged lipopolymer and aminopropanediol distearoyl (DS). No new matter has been added.

Claim 28 has been amended to recite, in part, that the a protein or polypeptide is "selected from the group consisting of Factor VIIa for treating trauma bleeding in hemophilia patients, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon $\gamma$, glucagon-*like* peptide 1 (GLP-1), and Copaxone," and to delete the consensus sequence. Support for claim 28 as amended can be found throughout the specification and claims as originally filed. No new matter has been added.

Claims 29-42 and 45 depend, either directly or indirectly, from independent claim 28. Claims 29-31, 36-42 and 45 have been amended to be in a form consistent with U.S. practice. No new matter has been added.

Claim 47 has been amended to recite "[a] method for treating a patient suffering from multiple sclerosis, comprising administering to the patient a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of Copaxone non-covalently bound to one or more colloidal particles, the one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the Copaxone is not

encapsulated in the one or more colloidal particles." Support for claim 47 as amended can be found throughout the specification and claims as originally filed. No new matter has been added.

Claim 54 has been amended to recite "[a] method for treating a patient suffering from *hemophilia*, comprising: administering to a patient in need thereof a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of *Factor VIIa* non-covalently bound to one or more colloidal particles, the one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein *Factor VIIa* is not encapsulated in the colloidal particles." (emphasis added) Support for amended claim 54 can be found throughout the specification and claims as originally filed.

Claim 57 has been amended to delete the recitation of "Factor VIIa." Support for amended claim 57 can be found throughout the specification and claims as originally filed. No new matter has been added.

New claim 59 recites "[a] pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon $\gamma$, glucagon-*like* peptide 1 (GLP-1) and Copaxone; and one or more colloidal particles having a mean particle diameter of from 0.03 to 0.4 microns, the one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic

polymer, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles." New claims 60-63 are each directly or indirectly dependent on independent claim 59. Support for new claims 59-63 can be found throughout the specification and claims as originally filed. No new matter has been added.

New claim 64 recites "[a] pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon $\gamma$, glucagon-*like* peptide 1 (GLP-1) and Copaxone; and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles. New claim 64 corresponds to claim 28 but does not recite the consensus sequence and does not recite Factor VIIa. New claims 65-68 are each directly or indirectly dependent on independent claim 64. Support for new claims 64-68 can be found throughout the specification and claims as originally filed. No new matter has been added.

New claim 73 recites "[a] pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon $\gamma$, glucagon-*like* peptide 1 (GLP-1) and Copaxone; one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer,

a second amphipathic lipid obtained from either natural or synthetic sources; and cholesterol, wherein the protein or polypeptide is non-covalently bound to the one or more colloidal particles and is not encapsulated in the one or more colloidal particles." New claim 73 corresponds to claim 28 but does not recite the consensus sequence and recites the limitations of claim 36, i.e., a second amphipathic lipid obtained from either natural or synthetic sources, as well as the limitations of claim 38, i.e., cholesterol. Support for new claim 73 can be found throughout the specification and claims as originally filed. No new matter has been added.

New claim 74 recites "[a] pharmaceutical composition for parenteral administration, comprising: a therapeutically effective amount of a protein or polypeptide selected from the group consisting of Factor VIIa, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon $\gamma$, glucagon-*like* peptide 1 (GLP-1) and Copaxone; and one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid selected from the group consisting of a carbamate-linked uncharged lipopolymer and aminopropanediol distearoyl (DS), the amphipathic lipid is derivatized with a biocompatible hydrophilic polymer, wherein the protein or polypeptide is non-covalently bound to one or more colloidal particles, and the protein or polypeptide is not encapsulated in the one or more colloidal particles." New claim 74 corresponds to claims 28 and 34-35 but does not recite the consensus sequence. Support for new claim 74 can be found throughout the specification and claims as originally filed. No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

***I. At page 3 of the Official Action, claims 44, 46-50, and 54-56 have been rejected under 35 USC § 112, first paragraph.***

The Examiner asserts that while the specification is "enabling for hemophilia, [it] does not reasonably provide enablement for any other diseases, disorders or conditions." *See* page 3 of the Official Action. The Examiner asserts that

In view of the following, this rejection is respectfully traversed.

Claims 44, 46, 48-49 and 55-56 have been canceled without prejudice or disclaimer rendering this rejection moot as to these claims.

With regard to claim 50, claim 50 has been amended to incorporate the limitations of claim 53, i.e., to recite that the protein or polypeptide is Copaxone. Claim 50 has been indicated allowable if rewritten in independent form to include all of the limitations of the base claim 50.

As to claim 47, claim 47 has been amended to recite treating a patient suffering from multiple sclerosis by administering to the patient a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of Copaxone non-covalently bound to one or more colloidal particles, the one or more colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein the Copaxone is not encapsulated in the one or more colloidal particles.

Regarding claim 54, claim 54 has been amended to recite, in part, a method for treating a patient suffering from hemophilia, comprising: administering to a patient in need thereof a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of Factor VIIa.

The enablement provision of the Patent Act requires that the patentee provide a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, first paragraph (2000). The purpose of this requirement is to ensure that "the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999); *see also* Donald S. Chisum, 3 *Chisum on Patents* § 7.01 (2002).

Accordingly, the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003); *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). "The key word is 'undue,' not experimentation.'" *Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Routine experimentation does not constitute undue experimentation. *See Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998). That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. *See, e.g., Nat'l Recovery Techs.*, 166 F.3d at 1196 ("The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation."); *Wands*, 858 F.2d at 736-37 ("Enablement is not precluded by the necessity for some experimentation such as routine screening."). "Nothing more than objective enablement

is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright,* 999 F.2d 1557 (Fed. Cir. 1993).

Although the ultimate determination of whether one skilled in the art could make and use the claimed invention without undue experimentation is a legal one, it is based on underlying findings of fact. *CFMT*, 349 F.3d at 1337. Furthermore, "[w]hether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands*, 858 F.2d at 737.

Some of these considerations, commonly referred to as "the *Wands* factors," include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.; see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that the *Wands* factors "are illustrative, not mandatory" and that what is relevant to an enablement determination depends upon the facts of the particular case).

With regard to the presently pending claims, Applicants respectfully submit that the specification, figures, and experimental examples, provide ample guidance to the skilled artisan in view of the state of the art at the time the application was filed, to make and use the claimed subject matter without undue experimentation.

Additionally, Applicants respectfully submit that that the court in *In re Wright* held that nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples.

Although the Examiner asserts that the specification "does not provide any examples as where the therapeutic polypeptides are modified or conjugated to the surface of PEG or liposome," Applicants respectfully point out to the Examiner that it is ***not necessary*** to indicate which specific residue binds to which specific molecule, but merely to ***teach a person having skill in the art how to carry out the claimed subject matter*** as required by *In re Wright.* In addition, "[d]etailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention." *See* MPEP at § 2164. The court in *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970), held that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *See* MPEP at § 2164.01(b).

Contrary to the Examiners assertion, the present specification describes and exemplifies, for example, at page 4, lines 6-9; page 5, line 25 to page 6, line 8; page 11, lines 5 to 21; and page 13, lines 13-20, suitable coupling reactions as well as the binding of proteins/polypeptides to liposomes. The specification, at page 4, lines 6-9, recites the following:

> ...the proteins or polypeptides interact non-covalently with the polymer chains on the external surface of the liposomes, and no chemical reaction is carried out to activate the polymer chains,...

In addition, the paragraph bridging pages 5 and 6 of the present specification, recites the following with regard to coupling reactions:

> A ***variety of known coupling reactions may be used for preparing vesicle forming lipids derivatized with hydrophilic polymers***. For example, a polymer (such as PEG) may be derivatized to a lipid such as phosphatidylethanolamine (PE) through a cyanuric chloride group. Alternatively, a capped PEG may be activated with a carbonyl diimidazole coupling reagent, to form an activated imidazole compound. A carbamate-linked compound may be prepared by reacting the terminal hydroxyl of MPEG...to yield a p-nitrophenyl carbonate. This product is then reacted with ...to yield the intermediate carbamate. The hydroxyl groups of the diol are acylated to yield the final product. A similar synthesis...as described in WO 01/05873. ***Other reactions are well know and are described, e.g. in the aforementioned U.S. 5,013,556, whose contents are incorporated herein by reference***. (emphasis added)

The present specification, in Examples 1-8, at page 11, lines 5-21, describes the following with regard to binding of proteins/peptides to liposomes:

> ***Binding of proteins/peptides to PEGylated liposomes.*** We analyzed the binding of proteins and peptides to PEGylated liposomes by Surface Plasmon Resonance (SPR) measurement using a Biacore instrument .... We immobilized proteins/peptides on a CM5 sensor chip ..., then injected PEGylated liposomes or control liposomes of the same size...and concentration and measured and analyzed the binding of protein/peptide to the flowed intake liposomes. PEGylated liposomes composed of POPC and DSPE-PEG-2000 bind to FVIII (Fig. 1a). The binding was dependent on the PEG polymer attached to DSPE lipid since two types of control liposomes composed of POPC and POPC:DSPE did not bind to FVIII (Fig. 1a). In addition, the binding was specific to FVIII, since the PEGylated liposomes did not bind to human serum albumin (HSA) (Fig. 1b). Binding analysis of a representative curve (Fig. 1a) using a two-site binding model indicates that the PEGylated liposomes bind to two sites on FVIII with association rate constants..., dissociation rate constants ... and affinity constant ...values...(Table 1). (emphasis added)

Further, the present specification, in Examples 9-10, at page 13, lines 13-20, describes the following with regard to a formulation of FIX and G-CSF with PEGylated liposomes:

> Formulation of FIX and G-CSF with PEGylated liposomes. PEGylated liposomes were formulated with either FIX (Octanine, Octapharma) or G-CSF (ProSpec-Tany TechnoGene Ltd, Nes Ziona, Israel) by dissolving the

protein with liposome solution (one ml liposome solution/200 units of FIX and 1 ml of liposome solution/10 µg of G-CSF). The vial was incubated on a SRT1 roller mixer rotate at 33 rpm, amplitude 16 mm (Stuart Scientific, Rehill, UK) for 10 minutes (G-CSF) or 60 minutes (FIX), at room temperature (20-25°C.).

In view of the foregoing and ***contrary to the Examiners assertion***, the present specification ***does describe and provide examples where the therapeutic polypeptides are modified or conjugated to the surface of PEG or liposomes.*** In summary, the presently claimed subject matter has been limited to a restricted list of proteins and to the diseases treatable by them. Thus, Applicants assert that the claimed subject matter is fully enabled by the specification within the meaning of 35 USC § 112, first paragraph. Should this rejection be maintained, the Examiner is specifically requested to address each point raised above.

In view of the foregoing, Applicants submit that the present specification enables the skilled artisan to make and use the full scope of claims 50 and 54 within the meaning of 35 USC § 112, first paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

***II. At page 27 of the Official Action, claims 28-42, 46-51 and 54-56 have been rejected under 35 USC § 112, first paragraph.***

The Examiner asserts that the specification does not clearly define or provide examples of what qualifies as compounds of the claimed invention. *See* page 16 of the Official Action. Further, the Examiner states that a protein or polypeptide having a consensus sequence S/T-X-L/I/V-I/V/Q/S-S/T-XX-E, where X may be any amino acid

lead to many different peptide consensus sequences. *See* page 29 of the Official Action.

In view of the following, this rejection is respectfully traversed.

Claims 46, 48-49, 51 and 55-56 have been canceled without prejudice or disclaimer rendering this rejection moot as to these claims. In addition, none of the pending claims, as amended or newly added, recite a consensus sequence.

The test under 35 U.S.C. § 112, first paragraph, for determining compliance with the written description requirement is whether the application clearly conveys that an applicant has invented the subject matter which is claimed. *In re Barker*, 194 USPQ 470, 473 (CCPA 1977); MPEP 2163. Also, the applicant must convey to the public what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything in common use or already known. MPEP § 2163. Lastly, the specification must convey that the applicant was in possession of the invention. MPEP § 2163.

With regard to claim 28, and claims 29-31 and 36-42 dependent thereon, claim 28 has been amended to delete the consensus sequence. Likewise, remaining claims 50 and 54 have been amended to delete the consensus sequence. Further, none of new claims 58-73 recite a consensus sequence.

In view of the foregoing, Applicants submit that the claims as amended satisfy the written description requirement of 35 USC § 112, first paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

***III. At page 33f the Official Action, claims 28-32, 36-37, 39-42 and 55-56 have been rejected under 35 USC § 102(b) as being anticipated by Baru et al.***

The Examiner asserts that the recitation of "...non-limiting examples of such proteins are coagulation factors such as prothrombin, Factor X and Factor V..." by Baru et al. meets the limitations of present claims 28-29, 32 and 36-37. In addition, in the previous Official Action at page 39, the Examiner admits that Baru et al. do "not teach the protein or polypeptide is selected from the group consisting of Factor VIIa, G-CSF, GM-CSF, interferon γ, GLP-1 and Copaxone." *See* page 34 of the Official Action.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

In view of the remarks set forth herein, this rejection is respectfully traversed.

Claims 55-56 have been canceled without prejudice or disclaimer rendering this rejection moot as to these claims.

None of the claims as amended or newly added recite a consensus sequence or recite any of "prothrombin, Factor X and Factor V."

In view of the foregoing, it is submitted that Baru et al. does not teach each and every element of the present claims, as required for anticipation under 35 USC § 102. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

***IV. At page 36 of the Official Action, claims 28-32, 36-37 and 39-42, 46, and 55-57 stand rejected under 35 USC § 103(a) as being anticipated by Baru et al.***

The Examiner asserts that it would have been obvious to the skilled artisan to try other proteins and polypeptides "since Baru reference teaches that the Factor VIII, prothrombin, Factor V and Factor X would be successful and phospholipids used do not encapsulate FVIII, so that smaller sized liposomes can be used which have a longer half-life in vivo."

In view of the remarks set forth herein, this rejection is respectfully traversed.

Claims 46 and 55-56 have been canceled without prejudice or disclaimer rendering this rejection moot as to these claims.

Claim 28 has been amended to recite, in part, "a therapeutically effective amount of a protein or polypeptide selected from the group consisting of ***Factor VIIa for treating trauma bleeding in hemophilia patients***, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon γ, glucagon-*like* peptide 1 (GLP-1), and Copaxone." (emphasis added)

Baru et al. do not teach or suggest a pharmaceutical composition containing such a protein or polypeptide. Baru et al. do not teach or suggest a pharmaceutical composition containing Factor VIIa for treating trauma bleeding in hemophilia patients as admitted by the Examiner who indicated claim 45 allowable. Claim 45 is dependent on claim 28 and recites "[t]he pharmaceutical composition of claim 28, wherein the polypeptide is Factor VIIa, and the composition may be used with inhibitors for the treatment of trauma bleeding in hemophilia patients." Claims 29-32 and 36-37, and 39-42 are each directly or indirectly dependent on independent claim 28.

Regarding claim 57, claim 57 has been amended to delete "Factor VIIa." It is submitted that Baru et al. do not teach or suggest a protein or polypeptide selected from the group consisting of granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), interferon $\gamma$, glucagon-*like* peptide 1 (GLP-1) and Copaxone, as recited in amended claim 57.

Further, Applicant's submit that new claims 58-74 are unobvious over the Baru et al. reference. Please *see* the remarks set forth above with respect to each of the new claims.

In view of the foregoing, it is submitted that nothing in Baru et al. renders the presently claimed subject matter obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

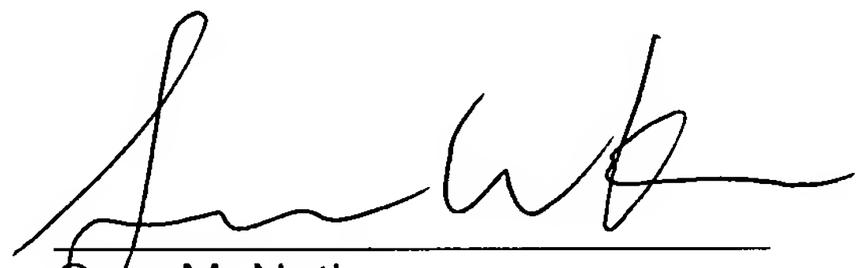
## *CONCLUSION*

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

**THE NATH LAW GROUP**



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